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Rapid Synthesis of Functionalized Indenes, Triazoles, and Glucocorticoid Receptor Modulators by Sequential Multicatalysis Cascade Reactions

Dhevalapally B. Ramachary,*[a] Rumpa Mondal,[a] and Chintalapudi Venkaiah[a]

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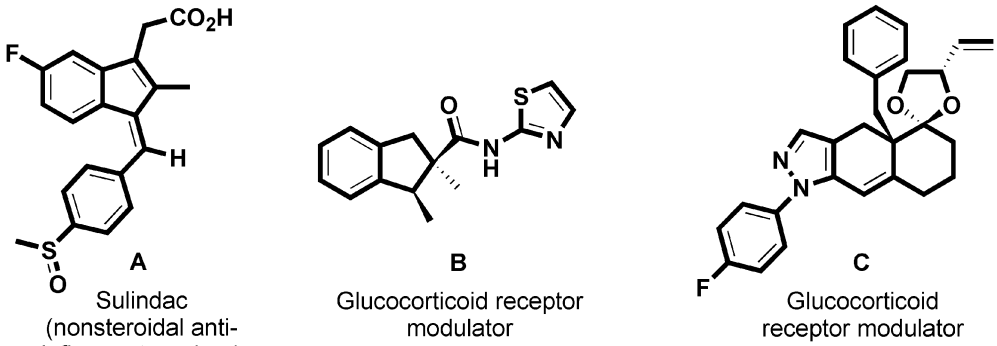
A general process for the synthesis of substituted indenes and 1,2,3-triazoles was achieved for the first time through a multicatalysis cascade reaction of 2-ethynylbenzaldehydes, CH acids, organic hydrides, and azides in the presence of a catalytic amount of L-proline/CuI/DIPEA. In this communication, we discovered the utilization of a single copper catalyst for two different reactions and shown synthetic application to the high-yielding synthesis of glucocorticoid receptor modulators.

Introduction

Functionalized indenes and 1,2,3-triazoles are an important class of carbo- and heterocycles. They exist as basic skeletons in a biologically active compounds and are used as drug intermediates in pharmaceuticals [Equation (1)].[1] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[2] Herein, for the first time we reported the one-pot synthesis of indenes and 1,2,3-triazoles from common substrates and catalysts through the "combination of multicomponent reactions (MCR) and multicatalysis cascade (MCC) reactions".[3]

The field of transition-metal-catalyzed cascade sequences continues to mature and develop. One area in particular that has witnessed significant interest over the past decade is the addition of active nucleophiles to an alkyne functionality under coinage metal catalysis.[4] More specifically, cascade reactions involving an alkyne functionality, wherein "soft" coinage metal ions (Cu, Ag, and Au) are employed to provide the necessary activation to trigger the cascade process.[4]

The combination of amino acids and suitably ligated coinage metal ion complexes could be identified as multicatalysts, and this would provide an ideal synthetic strategy compared to cellular reactions.[4a] Herein and for the first time, we propose that the iminium activation of aldehydes, the self-activation of olefins, and the simultaneous activation of metal ion alkynes could be combined in a cascade sequence, constituting a new carbocyclization method to furnish indenes through a Conia–ene reaction[5] and a new heterocyclization method to furnish 1,2,3-triazoles through



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[3+2] cycloaddition from common substrates and catalysts (Scheme 1). With many points of diversity present in the products, this MCC process would be a powerful method for the generation of indene and 1,2,3-triazole libraries and

[a] School of Chemistry, University of Hyderabad, Hyderabad 500046, India
Fax: +91-40-23012460
E-mail: ramsc@uohyd.ernet.in

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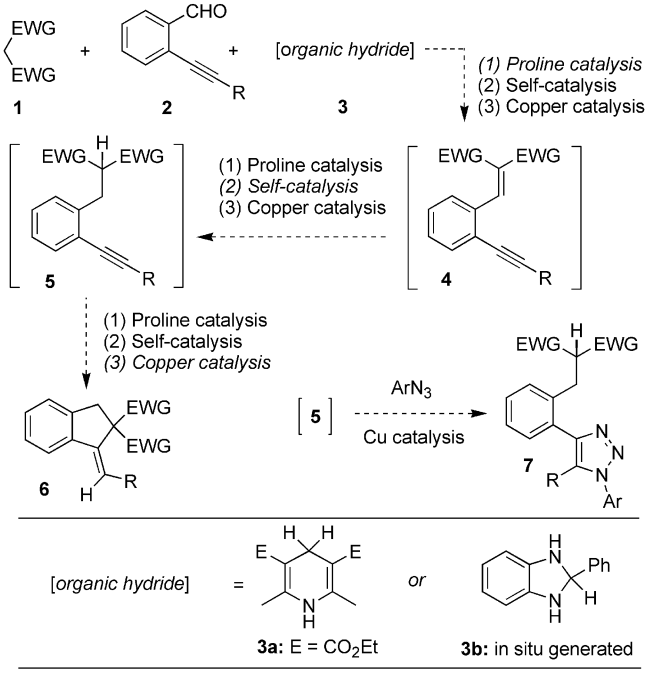
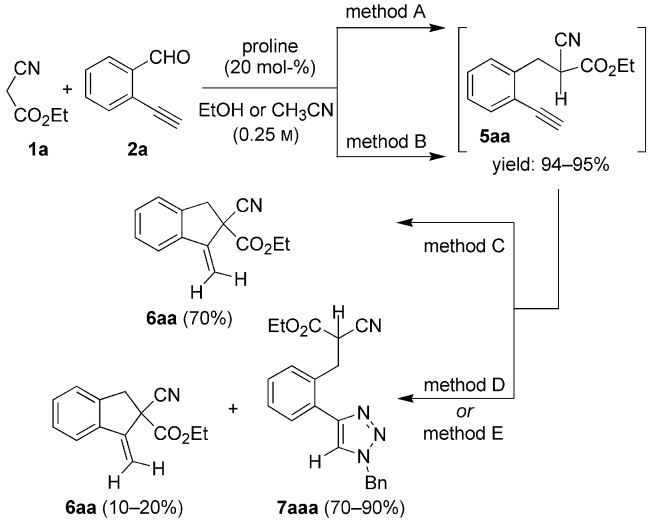
indene-based target synthesis [Equation (1) and Scheme 1]. Herein, we report our findings regarding these new MCC reactions and application to the high-yielding synthesis of glucocorticoid receptor modulators.



Scheme 1. MCC approach to functionalized indenes and triazoles.

Results and Discussion

We initiated our MCC studies by optimizing an olefination, hydrogenation, and cyclization sequence of **1a**, **2a**, **3a/3b**, and BnN_3 (**a**) by using different conditions, and some representative results are shown in Scheme 2. We found that L-proline readily catalyzes the olefination of **2a** with **1a** to furnish active olefin **4aa**,[6] which upon in situ treatment with Hantzsch ester **3a** produced hydrogenated product **5aa** with very good yield in EtOH, *t*BuOH, or CH_3CN at 25 °C for 24 h. The same reaction with in situ generated 2-phenyl-2,3-dihydro-1*H*-benzoimidazole (**3b**) also furnished product **5aa** with 95% yield in protic solvents. The optimum conditions involved the use of 20 mol-% catalyst in cascade olefination/hydrogenation reaction of **1a**, **2a**, and **3a/3b** in EtOH, *t*BuOH, or CH_3CN at 25 °C to furnish **5aa** in very good yield (see Scheme 2). After the successful synthesis of **5aa**, we decided to investigate suitable conditions to catalyze the carbocyclization of **5aa** in one-pot as shown in Scheme 2 and Table S1 (Supporting Information). Interestingly, reaction of **5aa** under the optimized conditions (15 mol-% of L-proline, 10 mol-% of CuI, and 2 equiv. of Cs_2CO_3) in CH_3CN at 25 °C for 0.5 h furnished indene **6aa** in 90% yield (Table S1, Supporting Information). Sequential one-pot combination of L-proline-/self-catalyzed olefination/hydrogenation reaction and CuI/L-proline/Cs_2CO_3-catalyzed carbocyclization of **1a**, **2a**, and **3a** in CH_3CN at 25 °C for 26 h furnished indene **6aa** with slightly reduced yield as shown in Scheme 2. The MCC reaction of **1a**, **2a**, and **3a** in CH_3CN at 25 °C for 2.5–12.5 h under the combination of pyrrolidine or morpholine with CuI/Cs_2CO_3 catalysis also furnished indene **6aa** in 64–70% yield (Equations S1 and S2, Supporting Information). Interestingly, reaction of **5aa** with CuI/L-proline/DIPEA in CH_3CN at 25 °C for 14 h furnished indene **6aa** in 86% yield, but there was no reaction with $CuSO_4$/Na–(+)-ascorbate in *t*BuOH and H_2O at 25 °C for 20 h as shown in Table S1, Entries 15–17 (Supporting Information).



Scheme 2. Optimization of the carbocyclization and heterocyclization reactions. Method A: Compound **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), L-proline (20 mol-%, 0.1 mmol); EtOH, *t*BuOH, or CH_3CN (0.25 M); 25 °C, 24 h. Method B: Compound **1a** (0.5 mmol), **2a** (0.5 mmol), L-proline (20 mol-%, 0.1 mmol), EtOH (0.25 M), 25 °C, 0.5 h. Then, **8** (0.5 mmol), PhCHO (0.5 mmol), 25 °C, 12 h. Method C: Compound **5aa**, CuI (0.05 mmol, 10 mol-%, 9.5 mg), Cs_2CO_3 (1 mmol, 2 equiv., 326 mg), CH_3CN (1.0 mL), 25 °C, 2 h. Method D: Compound **5aa**, BnN_3 (**a**) (1.0 mmol, 2 equiv.), CuI (0.05 mmol, 10 mol-%, 9.5 mg), DIPEA (30 mol-%), CH_3CN (1.0 mL), 25 °C, 6 h. Method E: Compound **5aa**, BnN_3 (**a**) (0.6 mmol, 1.2 equiv.), $CuSO_4 \cdot 5H_2O$ (0.1 mmol, 20 mol-%, 25 mg), Na–(+)-ascorbate (0.2 mmol, 40 mol-%, 40 mg), H_2O (1.0 mL), *t*BuOH (1.0 mL), 25 °C, 3 h.

After testing the sequential one-pot olefination/hydrogenation and carbocyclization or Conia–ene reaction of **1a**, **2a**, and **3a** under L-proline/CuI/base catalysis, we further investigated the intermolecular [3+2] cycloaddition of olefination/hydrogenation product **5aa** with BnN_3 (**a**) to furnish 1,2,3-triazole **7aaa** in one pot under the same catalytic conditions as shown in Scheme 2. Interestingly, the sequential one-pot reaction of in situ generated **5aa** with BnN_3 (**a**) (2 equiv.) under the optimized conditions [15 mol-% of L-proline, 10 mol-% of CuI, 30 mol-% of DIPEA] in CH_3CN at 25 °C for 6 h furnished 1,2,3-triazole **7aaa** in 70% yield and indene **6aa** in 20% yield (Scheme 2). In a similar manner, sequential one-pot combination of L-proline/self-catalyzed olefination/hydrogenation reaction and $CuSO_4$/Na–(+)-ascorbate-catalyzed heterocyclization of **1a**, **2a**, **3a**, and BnN_3 (**a**) in *t*BuOH and H_2O at 25 °C for 27 h furnished 1,2,3-triazole **7aaa** in 90% yield and indene **6aa** in 10% yield (Scheme 2).

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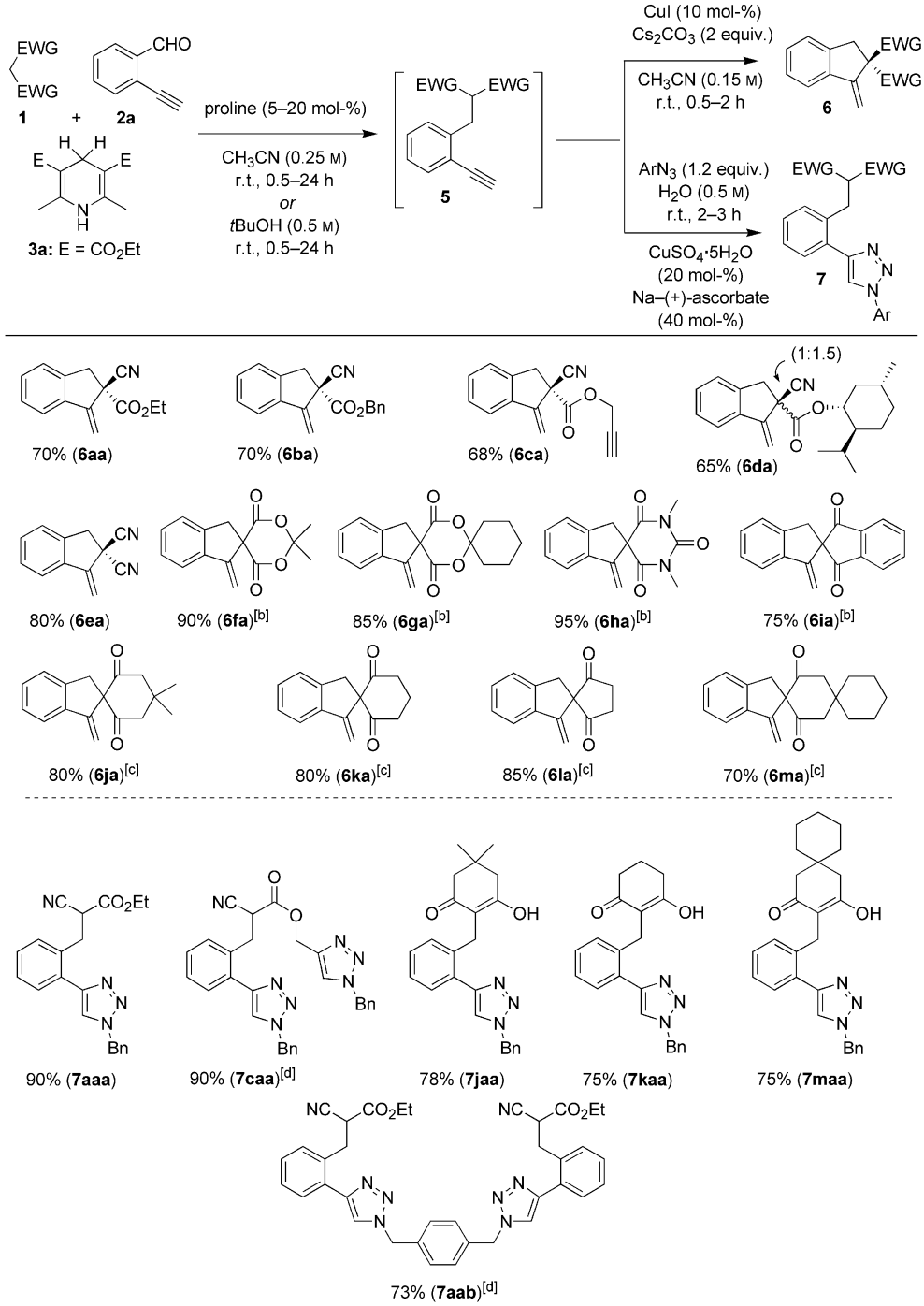
With the optimized reaction conditions in hand, the scope of the MCC reactions was investigated. A variety of CH acids **1a**–**m** were treated with **2a** (1 equiv.) and **3a** (1 equiv.) under sequential catalysis of L-proline (5 to 20 mol-%) and CuI/Cs_2CO_3 or CuI/Et_3N in CH_3CN at 25 °C for 0.5 to 2 h (Table 1). Acyclic and cyclic CH acids **1a**–**m** generated the expected Conia–ene products **6** with excellent yields (Table 1). Reaction of a menthol derivative of CH acid **1d** with **2a** and **3a** under L-proline/CuI/Cs_2CO_3 catalysis furnished (–)-**6da**, but unfortunately only 20 %*de* was observed (Table 1, Entry 4). Interestingly, reaction of cyclic CH acids **1f**–**i** with **2a** and **3a** under L-proline/CuI catalysis and the reaction of CH acids **1j**–**m** with **2a** and **3a** under L-proline/CuI/Et_3N catalysis furnished the mono-

Table 1. One-pot synthesis of indene **6** and 1,2,3-triazole products **7**.[a]



[a] Yield refers to the column-purified products. [b] Cs_2CO_3 was not used. [c] Et_3N (30 mol-%) was used instead of Cs_2CO_3. [d] Reaction time was 12 h.

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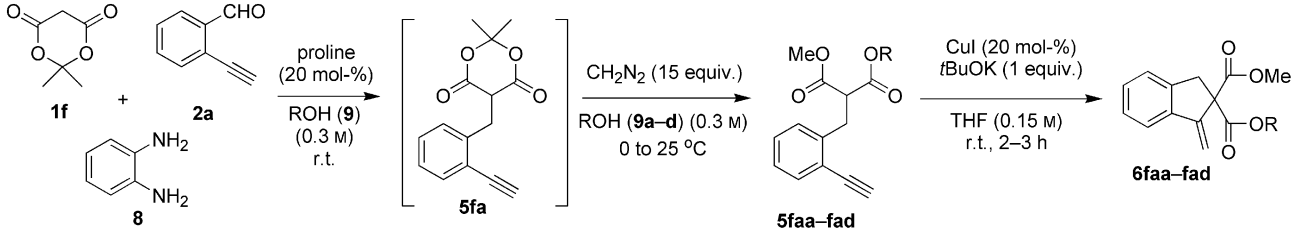
spiro and dispiro compounds **6fa**–**ma** as major products in 70–95% yields, which are sesquiterpenoid analogues (Table 1). Possibly as a result of the highly acidic nature of cyclic CH acids **1f**–**m** compared to acyclic CH acids **1a**–**e**, for compounds **5fa**–**ma** the Conia–ene reaction, which was performed under L-proline/CuI or L-proline/CuI/Et_3N catalysis, proceeded without the use of a strong base, as shown in Table 1. The structures of products **6aa**–**ma** were confirmed by NMR spectroscopic analysis; the structure was finally confirmed by X-ray structure analysis of **6ga** (Figure S1, Supporting Information).[7]

We further extended the three-component reaction into four-component heterocyclization reaction of **1**, **2a**, **3a**, and ArN_3 (**a**) and (**b**) for the synthesis of 1,2,3-triazoles **7** by L-proline/$CuSO_4$/Na–(+)-ascorbate catalysis in one-pot as shown in Table 1. The heterocyclization reaction of **1c** with **2a** and **3a** under L-proline/self-catalysis in *t*BuOH at 25 °C for 24 h furnished the cascade olefination/hydrogenation product **5ca**[6] in 99% conversion, which upon in situ treatment with BnN_3 (**a**) under $CuSO_4$/Na–(+)-ascorbate catalysis in *t*BuOH and H_2O at 25 °C for 12 h selectively furnished 1,2,3-triazole **7caa** in 90% yield (Table 1). In a similar manner, treatment of in situ generated **5ja**, **5ka**, and **5ma**[6] with BnN_3 (**a**) under $CuSO_4$/Na–(+)-ascorbate catalysis in *t*BuOH and H_2O at 25 °C for 2–3 h in one pot furnished 1,2,3-triazoles **7jaa**, **7kaa**, and **7maa** in 75–78% yield, which are useful starting materials for pharmaceutical drug analogs **C** [see Equation (1)].[3a] Interestingly, reaction of in situ generated **5aa** with 1,4-bis(azidomethyl)benzene (**b**) under $CuSO_4$/Na–(+)-ascorbate catalysis in *t*BuOH and H_2O at 25 °C for 12 h in one pot furnished 1,2,3-triazole **7aab** in 73% yield, which could be a useful starting material for the generation of medium-sized rings. In all heterocyclization reactions, 10–15% of carbocyclization products **6** were furnished.

With synthetic applications in mind, we further extended the application of the three-component carbocyclization reaction to the synthesis of dialkyl 1-methyleneindan-2,2-dicarboxylates **6faa**–**fad** in good yields (Table 2). Herein, we utilized the in situ generation and esterification of methoxycarbonyl ketenes with alcohols for the sequential one-pot synthesis of malonates **5faa**–**fad** from the olefination/hydrogenation/alkylation/ketenization/esterification (O/H/A/K/E) reactions of **2a**, Meldrum's acid (**1f**), *o*-phenylenediamine (**8**), diazomethane, and alcohols **9a**–**d** through iminium and self-catalysis in one pot.[3e] Interestingly, the L-proline/self-catalyzed cascade olefination/hydrogenation reaction of **1f** and **2a** (2 equiv.) with **8** in methanol (**9a**) at 25 °C for 0.5 h furnished **5fa** in >99% conversion, which upon in situ treatment with ethereal diazomethane at 0 → 25 °C for 6 h furnished expected malonate **5faa** in 87% yield (Table 2, Entry 1). In a similar manner, we synthesized three more nonsymmetrical malonates **5fab**–**fad** in good yield by performing the sequential O/H/A/K/E reactions in EtOH (**9b**), *t*BuOH (**9c**), and BnOH (**9d**) solvents (Table 2, Entries 2–4).

After successful preparation of malonates **5faa**–**fad**, we tested the carbocyclization reaction of **5faa** under one of the optimized conditions (15 mol-% of L-proline, 10 mol-% of CuI, 2 equiv. of Cs_2CO_3, THF or CH_3CN, 25 °C, 12 h; Table S1, Supporting Information). Interestingly, we did not observe the formation of the product under these conditions and only starting material **5faa** was isolated. When we applied the carbocyclization conditions of 30 mol-% *t*BuOK with 10 mol-% of CuI in THF at 25 °C for 12 h on **5faa**, the formation rate of **6faa** was very slow. When we increased the catalyst loading up to 20 mol-% of CuI and 1 equiv. of *t*BuOK in THF at 25 °C for 2 h, indene **6faa** was furnished in 80% yield (Table 2, Entry 1). In a similar manner, we synthesized three more nonsymmetrical indenes

Table 2. Synthesis of indene products **6** through six reactions in one pot.[a]



Entry	ROH	Time [h]		Product	Yield [%][a]	Entry	Time [h]	Product	Yield [%][a]
		O/H step	A/K/E step						
1	MeOH (**9a**)	0.5	6	**5faa**	87	1	2	**6faa**	80
2	EtOH (**9b**)	0.5	2	**5fab**	85	2	2	**6fab**	75
3	*t*BuOH (**9c**)	0.5	2	**5fac**	63	3	2	**6fac**	60
4	BnOH (**9d**)	0.5	6	**5fad**	85	4	2	**6fad**	70
5[b]	MeOH (**9a**)	0.5	6	**5faa**	99[c]	5[b]	3	**6faa**	70

[a] Yield refers to the column-purified products, and **2a** was used as two equivalents. [b] Reaction was performed in a sequential one-pot manner. [c] Conversion.

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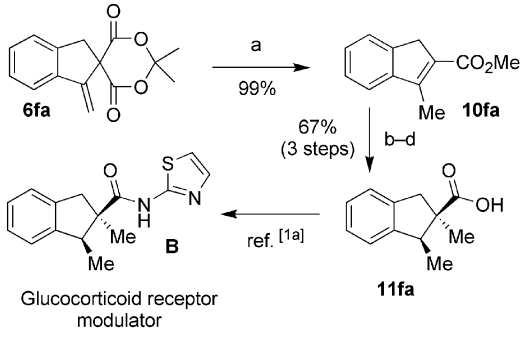
6fab–fad in good yields by using the above conditions on **5fab–fad** (Table 2, Entries 2–4). Finally, sequential combination of cascade O/H/A/K/E and carbocyclization reactions was performed in one-pot to furnish indene **6faa** in 70% yield (Table 2, Entry 5). Compound **6fad** could be a suitable intermediate for the synthesis of pharmaceuticals **A** and **B** [see Equation (1)], which emphasizes the value of this cascade approach.

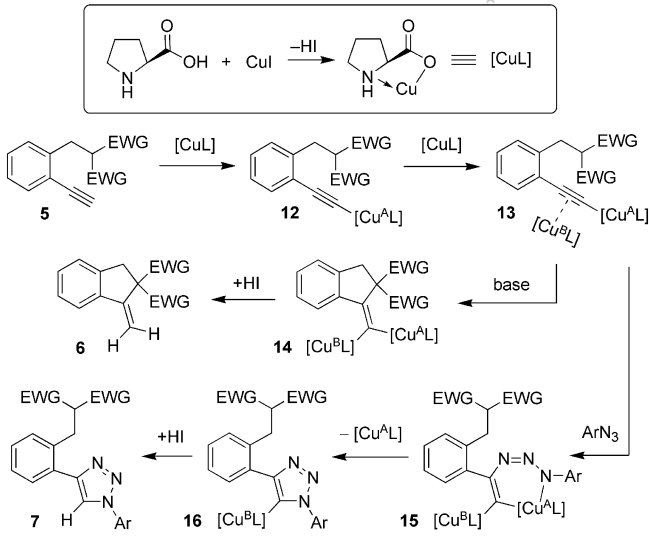
With pharmaceutical applications in mind, we synthesized drug intermediate **11fa** through **10fa** from MCC reactions (Scheme 3). Recently, **11fa** was used as a key intermediate for the total synthesis of glucocorticoid receptor modulator **B** (Scheme 3).[1a] Herein, by the combination of cascade olefination/hydrogenation/carbocyclization, base-induced decarboxylative isomerization, hydrogenation, alkylation, and hydrolysis reactions, we prepared **11fa** by using only four synthetic steps with an overall yield of 66% and >90%*de* (Scheme 3). Synthesis of key intermediate **10fa** through the MCC reactions is evidently more advantageous over the existing methods where expensive heavy metal catalysts (Pd, Co, Re, and Ru, etc.) or costly starting materials are used.[8]



Scheme 3. High-yielding synthesis of glucocorticoid receptor modulator. Reagents and conditions: (a) KOH (1 equiv.), MeOH (0.05 M), 65–75 °C, 1 h, 99%; (b) 10% Pd/C (5 mol-%), EtOAc (0.1 M), 25 °C, 12 h, 99%; (c) DIPA (2.5 equiv.), *n*BuLi (2.2 equiv.), MeI (4.5 equiv.), THF (0.25 M), –80 °C, 12 h, 88–90%; (d) 10% aqueous KOH (1 equiv.), MeOH (0.25 M), 100 °C, 12 h, 75%.

The possible common mechanism for the synthesis of **6** and **7** from **5** with or without azides under L-proline/CuI/base catalysis is illustrated in Scheme 4. In the first step, catalyst L-proline selectively reacts with CuI to generate bidentate copper species [CuL], which is an active Cu^{I} species that reacts with acetylenes.[4a] In the following second step, in situ generated [$Cu^{A}L$] selectively reacts with cascade olefination/hydrogenation product **5** to generate copper acetylide **12**. Mononuclear copper acetylide **12** further reacts with another active Cu^{I} species through π bonding to generate dinuclear alkynyl copper(I) complex **13**, which is more reactive than **12** in heterocyclization reactions with azides, as revealed by kinetic data and DFT calculations obtained and performed by Fokin et al.[9]

Dinuclear alkynyl copper(I) complex **13** has dual activation modes, as it can react with two kinds of nucleophiles (soft and hard; Scheme 4). Base-induced in situ generated soft carbanion can undergo intramolecular cyclization to



Scheme 4. Proposed reaction mechanism.

furnish dinuclear olefin **14**, which upon oxidative addition with HI followed by reductive elimination furnished expected carbocyclization product **6**. Intermolecular concerted [3+3] cycloaddition of active species **13** with hard alkyl azide heteronucleophiles can generate cupracycle **15** in the rate-determining step, which further undergoes reductive elimination to furnish mononuclear olefin **16**. Oxidative addition of **16** with HI followed by reductive elimination furnished expected heterocyclization product **7**. *From the successful demonstration of two kinds of cyclizations on single substrate* ***5*** *under common copper catalysis, we have provided possible support to the existence of dinuclear alkynyl copper(I) complex* ***13*** *in click reactions.*[9] π-Bonding of second copper complex [$Cu^{B}L$] with **12** is crucial and it acts as a Lewis acid for the intramolecular carbocyclization reaction; also it will increase the rate of the reaction by stabilizing newly formed cupracycle **15** in heterocyclization reactions with organic azides (Scheme 4). Further experimental support for the existence of dinuclear alkynyl copper(I) complex **13** in MCC reactions can be found in the Supporting Information.

Conclusions

In summary, for the first time we have developed two kinds of cyclization reactions that proceed in good yields with high selectivity by using L-proline/CuI/base as the common catalyst on common substrates. Furthermore, we have given possible support to the existence of dinuclear alkynyl copper(I) complex **13** in click reactions by demonstrating the two kinds of cyclizations on a single substrate. Many of the achiral building blocks (i.e., **6aa**, **6fa**, **7jaa**, **7kaa**, **7maa**, **6fad**, and **11fa**) prepared through the MCC reactions are illustrated to have direct application in pharmaceuticals. Further work is in progress to develop an asymmetric version of this chemistry.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, characterization data for

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new products, and complete details about the synthesis of new products.

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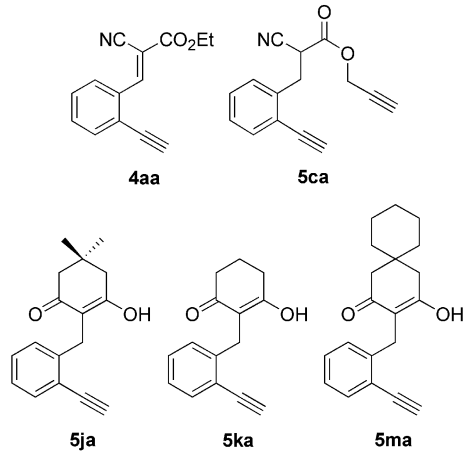

[7] CCDC-727395 (for **6ga**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information for crystal structure data.

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